201-14450

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Christine Todd Whitman
Administrator, US EPA
PO Box 1473
Merrifield, VA 22 116

May 2, 2003

Re: Chemical Right-to-Know HPV Chemical Challenge Program

Dear Administrator Whitman:

On behalf of Arch Chemicals, Inc. (Arch), I am pleased to submit the test plan and robust summaries for hydroquinone bis(2-hydroxyethyl) ether (CAS No. 104-3 8-1).

Enclosed with this letter are two copies of the test plan and robust summaries – one in hard copy and one on computer diskette in Microsoft Word format. The HPV registration number for Arch is

Arch understands that this information will be posted on the Internet for comments for a period of 120 days. Please forward comments to me at the above address.

Sincerely yours,

Steven J. DABT, CIH

201-14450A

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN

FOR

HYDROQUINONE bis(2-HYDROXYETHYL)ETHER

CAS NO. – 104-38-1

PREPARED BY:

ARCH CHEMICALS, INC.

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OVERVIEW

Arch Chemicals, Inc. (Arch) hereby submits for review and public comment the test plan for hydroquinone bis(2-hydroxyethyl)ether (HQEE; CAS # 104-38-1) under the Environmental Protection Agency's High Production Volume Chemical Challenge Program. It is the intent of Arch to use existing data, data from a structurally similar compound and estimated values using predictive computer models acceptable to EPA to adequately fulfill the Screening Information Data Set (SIDS) for the physical/chemical endpoints, environmental fate, ecotoxicity and human health-related toxicology.

HQEE is produced using hydroquinone and ethylene oxide and is used for polyurethane reactions as a chain extender. Chain extenders are low molecular weight substances that are capable of reacting with isocyanate groups to produce polyurethanes. HQEE has attained commercial significance for cast polyurethane elastomers as well as in thermoplastic elastomers to produce polyurethanes. These polyurethanes are very resistant to mechanical abrasion. The reaction using HQEE to produce polyurethanes is performed under temperature-controlled conditions in a polyurethane mixing and metering unit. This unit feeds components into the mixing head where the reaction between the isocyanate and HQEE begins. The reaction is completed in a closed mold to prevent reaction with atmospheric moisture. This unit is a sealed system because any exposure to moisture would compromise the reaction between HQEE and the isocyanate. The nature of this operation allows for very tight control of the HQEE; thus employee exposure to this material is low.

This chemical is not sold to the individual consumer. Its uses are in the industrial workplace where exposures are tightly controlled.

TEST PLAN SUMMARY

Hydroquinone bis(2-hydroxyethyl)ether CAS # 104-38-1	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	-	Y	N	Y	N
Boiling Point	Y	-	-	Y	N	Y	N
Vapor Pressure	Y	-	-	Y	N	Y	N
Partition Coefficient	Y	-	-	Y	N	Y	N
Water Solubility	Y	-	-	Y	N	Y	N
ENVIRONMENTAL FATE DATA							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y	Y	-	-	Y	Y	N
Biodegradation	Y	N	-	N	N	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICOLOGICAL DATA							
Acute Toxicity to Fish	Y	Y	-	-	Y	Y	N
Acute Toxicity to Aquatic Invertebrates	Y	Y	-	-	Y	Y	N
Toxicity to Aquatic Plants	Y	-	-	Y	N	Y	N
MAMMALIAN TOXICOLOGICAL DATA							
Acute Toxicity	Y	N	-	-	Y	Y	N
Genetic Toxicity							
Mutation	Y	-	Y	-	N	Y	N
Chromosome Aberration	Y	-	Y	-	N	Y	N
Repeated Dose Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	-	Y	-	Y	Y	N
Developmental Toxicity	Y	-	Y	-	Y	Y	N

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physical/Chemical Endpoints

Melting Point – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Boiling Point – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Vapor Pressure – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Partition Coefficient – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Water Solubility – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Conclusion – All endpoints have been satisfied by the utilization of data obtained from the various physical/chemical data modeling programs. The results from the utilization of these computer modeling programs are recognized by EPA as acceptable in lieu of actual data or values obtained from literature references. Thus, no new testing is needed in the area of physical/chemical properties.

B. Environmental Fate Endpoints

Photodegradation – A value for this endpoint was obtained using a computer estimation model (EPIWIN, Version 3.10.).

Stability in Water – This endpoint has been satisfied by a study that was conducted according to OECD guidelines (OECD guideline number 111) and GLP assurances.

Biodegradation – This endpoint was satisfied by data generated according to the Zahn-Wellens/EMPA test for inherent biodegradability (OECD guideline number 302B). This testing was conducted according to GLP assurances.

Fugacity – A value for this endpoint was obtained using the EPIWIN Level III portioning computer estimation model (EPIWIN, Version 3.10.).

Conclusion – All endpoints have been satisfied using actual data or through the use of EPA-acceptable estimation models.

C. Ecotoxicity Endpoints

Acute Toxicity to Fish – This endpoint was satisfied by data generated in a 96-hour bioassay using the fathead minnow. The concentrations of the test material were analytically measured at the start and end of the study. The study was conducted under OECD guidelines (OECD guideline number 203) and according to GLP assurances.

Acute Toxicity to Aquatic Invertebrates – This endpoint was satisfied by data generated in a 48-hour bioassay using the species, *Daphnia magna*. The concentrations of the test material were analytically measured at the start and end of the study. The study was conducted under OECD guidelines (OECD guideline number 202) and according to GLP assurances.

Toxicity to Aquatic Plants – A value for this endpoint was obtained using a computer program for estimating the ecotoxicity of industrial chemicals based on structure-activity relationships (Nabholz et al, 2001).

Conclusion – All endpoints have been satisfied using actual data or through the use of EPA-acceptable estimation models. No additional testing is needed in the area of ecotoxicity.

D. Mammalian Toxicological Endpoints

Acute Toxicity – This endpoint was satisfied by data generated via two routes of exposure, oral gavage and dermal application. One study per exposure route was performed and each was conducted as a limit test. Both studies were conducted according to currently accepted scientific methodology and GLP assurances.

Repeat Dose Toxicity – This endpoint was satisfied using data generated in a 28-day study via the oral (feed incorporation) route of exposure. The study was conducted according to OECD guidelines (TG-407) and GLP assurances.

Genetic and Reproductive/Developmental Toxicity – Data do not exist for these endpoints. However, the genetic toxicity (mutation or chromosome aberration) and reproductive/developmental toxicity of HQEE may be predicted from data generated on a structurally similar analog, hydroquinone monomethyl ether (HQMME, CASRN 150-76-5) (Florin et al., 1980; Bartsch et al., 1980; USFDA, 1997). The justification for using HQMME as an analog to satisfy the requirement for data for these endpoints for HQEE is based on the following comparisons for which information or data exist either from studies or from EPA-acceptable computer estimation models for both compounds:

- Molecular weight

  The molecular weight of HQMME is 124. That of HQEE is 198.

- Molecular structure

  A key factor supporting acceptability for use of an analog to predict toxicity is structural similarity. HQMME and HQEE are alkylether-substituted hydroquinones. The former compound is a mono-substituted methylether derivative while the latter compound is a di-substituted hydroxyethylether derivative. Thus, the functional groups attached to the aromatic ring are hydroxy, low molecular weight alkoxy, or low molecular weight hydroxyalkoxy groups.

- Log octanol/water partition coefficient

  This value for HQMME is 1.34 (Camilleri et al., 1988). The value for HQEE is 0.61 (KOWWIN v.1.66).

- Water solubility

  The water solubility of HQMME is 40 g/l (Chemicals Inspection and Testing Institute, 1992). The water solubility of HQEE is 13.4 g/l (WSKOW v1.40).

- Biodegradation

  HQMME and HQEE are inherently biodegradable under aerobic conditions. After 28 days contact time, there was greater than 95% degradation of each compound (Chemicals Inspection and Testing Institute, 1992 (HQMME); Lawrence and Ruffing, 1995 (HQEE)).

- Acute toxicity to fish

  The 96-hour LC_{50} to fathead minnow (*Pimephales promelas*) for HQMME (Geiger et al., 1985) and HQEE (Lawrence and Hirsch, 1995) is 110 mg/l and >1043.7 mg/l, respectively.

- Acute toxicity to aquatic invertebrates

  The 48-hour EC_{50} (immobilization) to *Daphnia magna* for HQMME (Bringman and Kuehn, 1982) and HQEE (Lawrence and Hirsch, 1995) is 7.2-19.3 mg/l and >100.2 mg/l, respectively.

- Acute toxicity to mammals from oral exposure

  The oral LD_{50} (rats, intubation) of HQMME is estimated to be 1630 mg/kg (Hodge, 1949). That for HQEE is >5000 mg/kg (Shepard, 1989).

- Repeated dose toxicity (28-day exposure) to mammals

  HQMME (Hodge, 1949) and HQEE (Hosenfeld and Hankinson, 1988) were administered to rats daily in the diet for 7 and 4 weeks, respectively. HQMME was administered at concentrations of 0.02, 0.1, 0.5, 2.0 or 5.0 %. HQEE was administered at

concentrations of 0.1, 0.3 or 1.0 %. No mortality was produced by either compound.

HQMME produced growth depression at dietary concentrations ≥ 0.5 %. Urinary glucose was elevated at ≥ 0.5 %. All hematological variables were comparable to control values at all concentrations. In animals fed ≥ 0.5 % organ weights were decreased, but organ to body weight ratios were comparable to controls. No histopathological change was observed to the heart, lungs, spleen, liver, kidneys, brain, testes and gastrointestinal tract that was compound related. The no-observed-adverse-effect level (NOAEL) in this study was 0.1 % in the diet, which corresponds to a dose of at least 100 mg/kg.

Following HQEE exposure no treatment-related clinical signs of toxicity were observed. There were no statistical body weight differences between any of the treated animals and control animals. The mean blood platelet count for the high-dose males was slightly less than for the control group. No other abnormalities in hematology were noted in the males. No hematological abnormalities were observed in any of the female animals. The clinical chemistry findings in all treated animals were comparable to controls. Relative kidney weights in low- and mid-dose females were lower ($p=0.02$), but not different from controls in the high-dose females. Absolute kidney weights for all treated female animals were similar to controls. No other organ weight differences were seen in any dose group for either sex. No compound related histopathological change was observed in any organs. The NOAEL in this study was 0.3 % in the diet (249 mg/kg) for male rats and 1.0 % (851 mg/kg) for females.

A review of the physical and toxicological data common to HQEE and HQMME was conducted. Both compounds may be predicted to have a low potential to accumulate in the body as indicated by the octanol/water partition coefficient and water solubility. In fact, HQMME was excreted mainly as conjugates of glucuronic and sulfuric acids and a very small amount was demethylated to give hydroquinone. The acid conjugates accounted for greater than 80 % of the metabolic profile and were excreted rapidly (Cosmetic Ingredient Review, 1985). HQEE would be expected to undergo metabolism to the carboxylic acid derivative and to be excreted rapidly. HQEE and HQMME would not bioaccumulate. Both compounds are readily biodegradable and would not accumulate in the environment. Data from aquatic and mammalian toxicity studies indicate that HQMME is generally more toxic than HQEE. Although HQMME is the more toxic quantitatively, there are no meaningful toxicological differences in the qualitative effects produced by these two compounds for the common endpoints for which data exist.

It is scientifically reasonable to predict that the toxicity of HQEE for genetic and reproductive/developmental toxicity would probably be less than but at least equal to the toxicity of HQMME. Therefore, the use of HQMME as an analog to predict the toxicity of HQEE for the endpoints of genetic and reproductive/developmental toxicity is appropriate.

Conclusion – The endpoints for acute toxicity and repeated dose toxicity have been satisfied with data from studies that were conducted utilizing methods that are scientifically current or according to an established guideline. The endpoints for genetic toxicology and reproductive/developmental toxicology have been satisfied using data from a structurally similar analog, HQMME. No additional testing is needed in the area of mammalian toxicity. Additional testing in the areas of genetic and reproductive/developmental toxicity would not yield any significant information and would result in needless use of animals, which is clearly against EPA policy.

SIDS DATA SUMMARY

Data to assess the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility) for HQEE were obtained from EPA-acceptable computer estimation modeling programs found in EPIWIN. These data indicate that HQEE is a solid at room temperature with a low vapor pressure. It has a low estimated octanol to water partition coefficient and is moderately soluble in water. The use of these modeled data meet the requirements of the various endpoints and thus there is no need for any additional testing to determine physicochemical properties.

Data to address endpoints for environmental fate of photodegradation, biodegradation and fugacity were obtained from actual studies or EPA-acceptable computer estimation modeling programs found in EPIWIN. As a result of its solubility in water and relatively low volatility, fugacity estimations predict that HQEE will distribute primarily to soil and water. Computer modeling predicts that HQEE would be expected to rapidly degrade in the atmosphere. Results from a biodegradation study indicate that HQEE undergoes rapid biodegradation and would not be expected to be persistent in the environment. The endpoint to determine acid/base-catalyzed hydrolysis has not been satisfied. Data for this endpoint will be based on OECD guideline number 111.

The data for aquatic toxicity endpoints were obtained from actual studies or EPA-acceptable computer estimation modeling programs found in ECOSAR (Nabholz et al., 2001). HQEE is of low toxicity to fish, daphnids and algae. The LC_{50} to fish (96 hours) is >1044 mg/l and the EC_{50} (immobility) to *Daphnia* (48 hours) is >100 mg/l. The EC_{50} (96 hours) to algae is 1672 mg/l.

The data to determine acute toxicity and repeated dose toxicity are from studies that were conducted according to acceptable scientific methodology (acute

toxicity) or an OECD test guideline (TG-407). The oral LD_{50} and dermal LD_{50} are greater than 5 g/kg and 2 g/kg, respectively.

HQEE was administered to rats in the diet at concentrations of 0.1, 0.3 or 1.0 % for 28 days. Following exposure no treatment-related clinical signs of toxicity were observed. There were no statistical body weight differences between any of the treated animals and control animals. The mean blood platelet count for the high-dose males was slightly less than for the control group. No other abnormalities in hematology were noted in the males. No hematological abnormalities were observed in any of the female animals. The clinical chemistry findings in all treated animals were comparable to controls. Relative kidney weights in low- and mid-dose females were lower ($p=0.02$), but not different from controls in the high-dose females. Absolute kidney weights for all treated female animals were similar to controls. No other organ weight differences were seen in any dose group for either sex. No compound related histopathological change was observed in any organs. The NOAEL in this study was 0.3 % in the diet (249 mg/kg) for male rats and 1.0 % (851 mg/kg) for females.

Hydroquinone monomethylether (HQMME) is serving as an analog to predict the genetic toxicity of HQEE. HQMME has been evaluated in two assays for mutagenicity, 1) Ames/*Salmonella* point mutation assay (two studies) and 2) *in vivo* micronucleus assay. HQMME was tested up to 496 µg/plate in *Salmonella* strains TA 98, 100, 1530, 1535 and 1537 with and without metabolic activation. HQMME did not produce mutations in this assay. The potential of HQMME to produce chromosomal aberrations was evaluated in the micronucleus assay using rats. Dermal exposure of HQMME for 6 months failed to induce micronuclei in the test animals. Thus, HQMME was judged to lack the potential to produce chromosomal aberrations.

HQMME is also serving as an analog to predict the reproductive/developmental toxicity of HQEE. Two studies were conducted to determine the potential of HQMME to affect fertility and reproductive performance. Both studies will be included in the robust summary because they are complimentary in the data that was generated from each. In the first study HQMME was administered once daily (6 hours/day) dermally to rats at 20, 40 or 80 mg/kg. Males were dosed for 4 weeks and females for 2 weeks prior to mating. All animals were dosed throughout the cohabitation period for a maximum of 3 weeks. Females were dosed through gestation day 7 and sacrificed on gestation day 15. Males were dosed through the day before the scheduled sacrifice. In males mating and fertility parameters and sperm quality were not affected by treatment. Testicular weights appeared to be decreased in high dose males, but histological examination of the testes revealed no treatment-related changes. In females estrous cycling, mating, fertility and intrauterine parameters were not affected by treatment. Post-implantation loss and mean numbers of viable embryos, corpora lutea and implantation sites were similar in treated and control groups. There were no treatment-related findings on gross necropsy. There was no treatment-related

histopathological change to male animals. The parental systemic NOAEL was determined to be 40 mg/kg/day; for reproductive performance it was considered to be greater than 80 mg/kg/day.

In the second study HQMME was administered once daily dermally (6 hours/day) to the back of rats. The material was applied at a rate of 12, 40 or 120 mg/kg to pregnant F_0 animals (gestation day 6-20). Dams were allowed to deliver naturally. At post-natal day 4, litters were culled and the F_1 animals were evaluated for physical and functional development and reproductive performance. F_1 animals were mated and F_2 fetuses were evaluated on gestation day 20. F_0 animals had dose-related irritation that was severe enough to recommend and proceed with sacrifice of dams and offspring during the first week of lactation. In F_1 animals, treatment-related effects were observed only at the maternally toxic high dose. In that group there was increased pup mortality, decreased pup body weight, and an increased incidence of clinical signs. Four high dose F_0 females had total litter loss between lactation days 1 and 5. Reduced F_1 survival was observed in high dose litters after post-natal day 1 and these pups also had reduced body weights. Estrous cycling in F_1 females and reproductive performance in F_1 animals was unaffected by treatment. Gravid uterine weights and F_2 fetuses were also unaffected. On gross necropsy, the only treatment-related finding in the F_0 dams was reddening, thickening and scabbing of skin at treated sites. No treatment-related gross pathological change was noted in the F_1 pups, F_1 adults and the F_2 pups. Based on this study, the maternal, neonatal, and developmental NOAELs were determined to be 40 mg/kg/day.

The developmental toxicity of HQMME was evaluated in rats and rabbits. In rats the test material was applied once daily to the skin of the back for 6 hours/day on days 6-15 of gestation. The dose rate was 20, 40 or 80 mg/kg/day. The dams exhibited no systemic signs of toxicity. The mean body weight in the high dose group was reduced and was significantly different from controls on gestation days 12-16. No significant differences were seen in numbers of viable or dead fetuses, post-implantation loss, pre-implantation loss, and numbers of corpora lutea and implantation sites. No external malformations or variations were observed. There were no treatment-related visceral or skeletal malformations at any dose. The systemic maternal NOAEL was 40 mg/kg/day and the NOAEL for developmental toxicity was greater than 80 mg/kg/day. In a second study rats were exposed to a daily dermal dose of HQMME on gestation days 1-20. No significant differences were observed between treated and control groups with respect to skeletal anomalies, post-implantation mortality, craniocaudal dimensions and weight of embryos, or placental weights. However, HQMME did produce embryo toxicity as demonstrated by an increase in pre-implantation loss. This study did not meet the requirements for reliability because only one dose of HQMME was used and it was reported only in abstract form. It is being included in the robust summary because embryo toxicity was observed.

In rabbits the test material was applied once daily to the skin of the back for 6 hours/day on days 6-18 of gestation. The dose rate was 4, 12 or 40 mg/kg/day. The dams exhibited no systemic signs of toxicity. No significant differences were seen in litter size, early or late resorptions, numbers of viable or dead fetuses, post-implantation loss, pre-implantation loss, number of corpora lutea, implantation sites, fetal body weights and sex ratio. In this study there were no statistically significant differences among treatment groups in fetal malformations; however, the mid and high dose groups did have an increased incidence of skeletal variations. A NOAEL of 4 mg/kg/day for teratogenicity in rabbits was established.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the systematic approach described by Klimisch et al. (1997). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. They are:

1. Reliable without restriction: Includes studies or data complying with Good Laboratory Practices (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

2. Reliable with restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

3. Not reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

4. Not assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

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General Information

CAS Number: 104-38-1
Common Name: Hydroquinone bis(2-hydroxyethyl)ether

II. Physical-Chemical Data

A. Melting Point

Test Substance

Identity: Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Remarks: Mean or weighted melting point

Method

Method: Estimation
Remarks: None

Results

Melting Point Value: 102.86°C
Remarks: None

Reference

MPBPWIN v1.40 (EPI Suite™ v.3.10). Downloadable at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm ©2000 U.S. Environmental Protection Agency.

Other

B. Boiling Point

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Remarks:	None

Method

Method:	Estimation
Remarks:	Adapted from Stein & Brown method

Results

Boiling Point Value:	343.86^{o}C
Remarks:	None

Reference MPBPWIN v1.40 (EPI Suite™ v.3.10). Downloadable at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm ©2000 U.S. Environmental Protection Agency.

Other

C. Vapor Pressure

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Remarks:	None

Method

Method:	Estimation
Remarks:	Mean of Antoine and Grain methods

Results

Vapor PressureValue:	6.63×10^{-7} mmHg @ 25^{o}C
Remarks:	None

Reference MPBPWIN v1.40 (EPI Suite™ v.3.10). Downloadable at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm ©2000 U.S. Environmental Protection Agency.

Other

D. Partition Coefficient

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Remarks:	None

Method

Method:	Estimation
Remarks:	None

Results

K_{ow}:	0.61
Remarks:	None

Reference KOWWIN v.1.66. (EPI Suite™ v.3.10). Downloadable at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm ©2000 U.S. Environmental Protection Agency.

Other

E. Water Solubility

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Remarks:	None

Method

Method:	Estimation
Remarks:	None

Results

Value:	13,360 mg/l
Temperature:	25°C
Remarks:	A K_{ow} of 0.61 was used in this estimation.

Reference

WSKOW v1.40 (EPI Suite™ v.3.10). Downloadable at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm ©2000 U.S. Environmental Protection Agency.

Other

III. Environmental Fate Endpoints

A. Photodegradation

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Remarks:	None

Method

Method:	Estimation
Test type:	Atmospheric oxidation
Remarks:	None

Results

Hydroxyl radicals reaction:	
OH Rate Constant:	40.9385 x 10^{-12} cm^3/molecule-sec
Half-life:	0.261 days (12-hr day; 1.5 x 10^6 OH/cm^3
Temperature:	25^0C
Ozone reaction:	No ozone reaction estimation was noted.
Remarks:	None

Conclusions The material is expected to rapidly degrade in the atmosphere.

Reference AopWin v1.90. (EPI Suite™ v.3.10). Downloadable at http://www.epa.gov/oppt/exposure/docs/episuitedl.htm ©2000 U.S. Environmental Protection Agency.

Other

B. Stability in Water

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	> 99%
Remarks:	None

Methods

Method:	OECD TG-111
Type:	Hydrolysis as a function of pH
GLP:	Yes
Year:	2003
Remarks:	Hydrolysis of HQEE was determined at 3 different pH values; 4.0, 7.0 and 9.0. The pH 4 solution was prepared as a 0.01 M sodium acetate buffer. It was prepared by weighing 0.82 grams of anhydrous sodium acetate into a l liter volumetric flask and adding 900 mL of distilled water. The pH was adjusted to 4.0 with concentrated acetic acid and diluted to the mark with distilled water. pH 7.0 solution was prepared as a 0.01 M phosphate buffer. It was prepared using 1.4 grams of potassium phosphate monobasic crystal per liter of solution. The pH was adjusted to 7.0 with 1 N sodium hydroxide and/or hydrochloric acid and diluted to the mark with distilled water. pH 9.0 solution was prepared as a 0.025 M sodium borate buffer. It was prepared by weighing 9.5 grams of sodium borate decahydrate into a 1 liter volumetric flask and adding 900 mL of distilled water. The pH was adjusted to 9.0 with sodium hydroxide and/or hydrochloric acid and diluted to the mark with distilled water. The buffers were autoclaved prior to use in order to remove any microbes and oxygen from the solutions. A preliminary test was conducted to determine the saturation concentration of the test material. It was determined to be 5,120 mg/l. For the main study the concentration of HQEE was 28 mg/l, which is less than the approximate half-saturation concentration and less than 0.01 M based on a molecular weight of 198. At each pH, 500 ml of test solution was subdivided into 33 vessels each containing 14 ml. The vessels were tightly capped, wrapped in aluminum foil to

exclude light, and incubated at 50 ± 1° C in a water bath. Three vessels were taken at each time point (0, 0.5, 1.0, 1.5, 3.25, 3.75, 24, 48, 72, 96, and 120 hours) and analyzed for the test substance. Appropriate controls were used as blanks for analysis.

Results

At pH 4, 7, and 9 the average measured concentration of the test article after 5 days residence in water at 50° C was 27.6, 29.1, and 29.2 mg/l, respectively. The data for all time points is presented in table 1. Each value is the mean ± standard deviation of 3 replicates.

Table 1. Measured Concentration of HQEE (mg/l)

Time (hours)	pH 4.0	pH 7.0	pH 9.0
0	28.4±0.1	28.2±0.3	28.2±0.5
0.5	28.5±0.3	28.2±0.3	28.6±0.3
1.0	28.4±0.2	28.5±0.5	28.7±0.4
1.5	28.3±0.1	28.5±0.5	28.7±0.5
3.25	28.5±0.1	28.7±0.2	28.2±0.1
3.75	28.5±0.1	28.2±0.4	28.5±0.5
24	28.3±0.2	28.3±0.1	28.5±0.2
48	28.4±0.1	28.7±0.2	28.7±0.4
72	28.0±0.2	28.7±0.3	28.7±0.3
96	27.9±0.2	29.0±1.8	28.6 ±0.3
120	27.6±0.3	29.1±0.4	29.2±0.4

Conclusions HQEE is considered to be hydrolytically stable ($t_{1/2}$ > 1 year) based on the recovery of > 90 % of the test article from 5 day old samples in water buffered to pH 4, 7, or 9.

Data Quality

Reliability: 1A

Remarks: Reliable without restrictions; Guideline study (OECD TG-111).

References

Ward, T. J., C. C. Rondon, and R. L. Boeri. 2003. HQEE [Hydroquinone bis(2-Hydroxyethyl)Ether], CAS # 104-38-1: Hydrolysis as a Function of pH. T. R. Wilbury Laboratories, Inc. Study Number 2565-AR. Marblehead, MA.

Other

C. Biodegradation

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	> 99.9%
Remarks:	None

Method

Method:	OECD TG-302B
Test type:	Zahn-Wellens/EMPA test for inherent biodegradability.
GLP:	Yes
Year:	1995
Contact time:	28 days
Inoculum:	Microorganisms obtained from mixed liquor suspended solids from Van Lare Waste Water Treatment Plant, Rochester, NY.
Remarks:	The test article solution (500 ml) was prepared in duplicate using 2-L Erlenmeyer flasks. The positive control solution (sodium benzoate) was prepared using a single Erlenmeyer flask. The theoretical concentration of test article and positive control was 50 mg DOC/L. Another flask served as a blank control. The vehicle was mineral nutrient solution. The incubation temperature was 21-22^0 C. All vessels were inoculated with 100 ml of the inoculum to achieve 0.2 – 1.0 g/L of suspended solids in the final test solution. The DOC, pH and dissolved oxygen were determined on days 1, 4, 6, 8, 11, 15, 18, 22, 25, 27 and 28. DOC concentrations were determined in triplicate using a Dohrmann DC-180 Carbon Analyzer. The instrument was calibrated using a 10 ppm organic carbon standard. The DOC concentrations were determined to nearest 0.1 mg/L and expressed as the arithmetic mean.

Results

Degradation %:	The starting DOC concentration of the test article solutions A and B and the positive control was 40.8 ppm, 42.6 ppm and 41.2 ppm, respectively. On day 28, DOC concentration for test article solutions A and B and the positive control was 1.0 ppm, 1.3 ppm and 3.4 ppm, respectively. These values

represent a loss of 97 % DOC for the test article and 92 % DOC for the positive control.

	Degradation Rate (%)	
Sample time (day)	Test Article	Positive Control
1	16	96
4	1	87
6	3	68
8	0	105
11	11	102
15	65	99
18	97	99
22	95	96
25	101	87
27	101	99
28	97	92

Classification: The test article is inherently biodegradable under the definition of this test.

Kinetic: Not stated

Breakdown products: Not stated

Remarks: The positive control had a DOC removal exceeding 70% within 14 days. This fulfills the requirements of a valid test. No protocol deviations were noted.

Conclusions

The results indicate that the test material undergoes rapid biodegradation and would not be expected to be persistent in the environment.

Data Quality

Reliability: 1A

Remarks: Reliable without restrictions; Guideline study (OECD TG-302B).

Reference

Lawrence, D. L. and C. J. Ruffing. 1995. Determination of Inherent Biodegradability (Biotic Degradation) Using the Zahn-Wellens/EMPA Test. Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY. Study No. EN-111-023646-1.

Other

D. Transport between Environmental Compartments (Fugacity)

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Remarks:	None

Method

Method:	Estimation
Model:	Level III Fugacity Model; EPIWIN: EQC from Syracuse Research Corporation
Remarks:	None

Results

Estimated distribution and media concentration:		Mass Amount (%)	Half-Life (hr)	Emissions (kg/hr)
	Air	0.00176	6.27	1000
	Water	43.7	360	1000
	Soil	56.2	360	1000
	Sediment	0.0754	1.44×10^3	0
Remarks:	Physical chemical values utilized in this model were default values obtained from the EPIWIN program.			

Reference

Level III Fugacity Model. (EPI Suite™ v.3.10). Downloadable http://www.epa.gov/oppt/exposure/docs/episuitedl.htm ©2000 U.S. Environmental Protection Agency.

Other

IV. Ecotoxicity

A. Acute Toxicity to Fish

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	>99.9% initial and 99.9% final, using gas chromatography with flame ionization detection
Remarks:	None

Method

Method:	OECD TG-203
Test type:	Acute static
GLP:	Yes
Year:	1995
Species/strain:	Fathead minnow (*Pimephales promelas*)
Analytical monitoring:	The concentration of the test substance was determined analytically using high performance liquid chromatography with an ultraviolet detector. The test substance was measured at study time 0 and 96 hours.
Exposure period:	96 hours
Statistical methods:	The LC_{50} and 95 % confidence level at various time points (24, 48, 72, and 96 hours) during the study were determined using the following three approaches: non-linear interpolation, moving average method and probit method.
Remarks:	The test organisms were exposed to 5 analytically determined concentrations that ranged from 86 to 1044.2 mg test article/l of water. The aquatic test was performed in seamless Pyrex glass 30.5 cm cuboidal chromatography jars, each containing 20 L of exposure solution. The light/dark cycle of the photoperiod was 16 hours on/8 hours off with a 20 minute transition period. The temperature in all test vessels remained at 20 ± 1^{o} C during the test. The pH and oxygen ranged from 8.0 to 8.6 and 8.6 to 9.2 mg/l, respectively. Observations for mortality and signs of stress were made during the study at 0, 2.5, 24, 48, 72 and 96 hours. After the measurements for physical parameters were performed at time 0, the minnows were placed into each of the replicate test article concentration vessels and replicate control vessels. They were

approximately 37 days old at the start of testing. Two replicates were used for each concentration with 10 minnows per vessel for a total of 20 fish per concentration. All organisms for this test were acclimated to the diluent water prior to the test since the same filtered-treated-tempered water and filtered, compressed air used for all laboratory water/aeration processes during the test were supplied continuously to the stainless steel rearing tanks. All organisms used in this test were maintained in this water for at least two weeks before being exposed to the test article.

Results

Analytical concentrations: Mean of values determined at 0 and 96 hours of test
Control – no test article detected
86 mg/l, 168.3 mg/l, 312.8 mg/l, 570.4 mg/l and 1044.2 mg/l.

Mortality:

Concentration (mg/l)	Percent Mortality Time (hours) 2.5	24	48	72	96
Control	0	0	0	0	0
86	0	0	0	0	0
168.3	0	0	0	0	0
312.8	0	5	5	5	5
570.4	0	0	0	0	0
1044.2	0	0	0	0	0

Values: LC_{50} (95% confidence limits) (mg/l)

24-hr	48-hr	72-hr	96-hr
>1043.7	>1043.7	>1043.7	>1043.7

NOEC (mg/l)

24-hr	48-hr	72-hr	96-hr
>1043.7	>1043.7	>1043.7	>1043.7

Remarks: None

Data Quality

Reliability: 1A
Remarks: Reliable without restrictions; Guideline study (OECD 203).

Reference	Lawrence, D. L. and M. P. Hirsch. An Acute Aquatic Effects Test with the Fathead Minnow, *Pimephales promelas* using Hydroquinone bis (2-Hydroxyethyl) Ether. Eastman Kodak Company, Rochester, NY. Study No. EN-430-023646-1; HAEL No. 94-0220. 1995.
Other	

B. Acute Toxicity to Invertebrates

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	>99.9% initial and 99.9% final, using gas chromatography with a flame ionization detector

Method

Method:	OECD TG-202
Type:	Acute static
GLP:	Yes
Year:	1995
Species/strain:	Water flea (*Daphnia magna*)
Analytical monitoring:	The concentration of the test substance was determined analytically using high performance liquid chromatography with ultra violet detection. The test substance was measured at study time 0 and 48 hours.
Exposure period:	48 hours
Statistical methods:	The LC_{50} and 95 % confidence level at various time points (24 and 48 hours) during the study were determined using the following three approaches: non-linear interpolation, moving average method and probit method.
Remarks	The test organisms were exposed to 5 analytically determined concentrations that ranged from 100.2 to 992.9 mg test article/l of water. The aquatic test was performed in 250-ml Pyrex glass beakers. The light/dark cycle of the photoperiod was 16 hours on/8 hours off with a 20 minute transition period. The temperature in all test vessels remained at 21^{o} C during the test. The pH and oxygen ranged from 8.1 to 8.3 and 8.4 to 8.9 mg/l, respectively. Observations signs of immobility and stress were made during the study at 0, 6, 24 and 48 hours. After the measurements for physical parameters were performed at time 0, neonate daphnids were placed into each of the replicate test article concentration vessels and replicate control vessels. Two replicates were used for each concentration with 10 daphnids per vessel for a total of 20 organisms per concentration. All daphnids for this test were acclimated to the diluent water prior to the test since the same filtered-treated-tempered water

and filtered, compressed air used for all laboratory water/aeration processes during the test were supplied continuously to the stainless steel rearing tanks. All organisms used in this test were maintained in this water for at least two weeks before being exposed to the test article.

Results

Analytical concentrations: Mean of values determined at 0 and 48 hours of test
Control – no test article detected
100.2 mg/l, 188.1 mg/l, 325.5 mg/l, 553.5 mg/l and 992.9 mg/l

Immobility:

Concentration (mg/l)	Percent Immobile Time (hours)			
	0	6	24	48
Control	0	0	0	0
100.2	0	0	5	15
188.1	0	0	0	40
325.5	0	0	0	0
553.5	0	0	0	20
992.9	0	0	0	25

Values:

EC_{50} (95% confidence limits) (mg/l)

24-hr	48-hr
>992.9	>100.2

NOEC (mg/l)

24-hr	48-hr
992.9	100.2

Data Quality

Reliability (Klimisch): 1A

Remarks: Reliable without restrictions; Guideline study (OECD TG-202).

Reference

Lawrence, D. L. and M. P. Hirsch. An Acute Aquatic Effects Test with the Daphnid, *Daphnia magna* using Hydroquinone bis (2-Hydroxyethyl) Ether. Eastman Kodak Company, Rochester, NY. Study No. EN-431-023646-1; HAEL No. 94-0220. 1995.

Other

C. Acute Toxicity to Aquatic Plants

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Remarks:	None

Method

Method:	Estimation
Test type:	96-hour EC_{50}
Organism:	Green Algae
Remarks:	None

Results

EC_{50} (96 hours):	1672 mg/l
Remarks:	None

Reference

Nabholz, J. V., Cash, G., Meylan, W. M. and Howard, P. H. 2001. ECOSAR: A Computer Program for Estimating the Ecotoxicity of Industrial Chemicals Based on Structure Activity Relationships, Version 0.99g. Washington, DC: Risk Assessment Division, Office of Pollution Prevention and Toxics, United States Environmental Protection Agency. Available from EPA web page at http://www.epa.gov/oppt/newchems/21ecosar.htm or http://www.epa.gov/oppt/exposure/docs/episuitedl.htm

Other

V. Mammalian Toxicity

A. Acute Toxicity – Entry 1 of 2

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	Not stated
Remarks:	None

Method

Method/guideline followed:	Not stated
Type:	Oral toxicity
GLP:	Yes
Year:	1989
Species/Strain:	Rat/Crl:CD (SD)BR
Sex:	Male/Female
Number of animals/ sex/dose:	5
Vehicle:	0.5% aqueous guar gum
Route of administration:	Oral (gavage)
Remarks:	One group of 10 rats (5M, 5F) was administered the test substance (25 % concentration in vehicle) at a dose of 5 g/kg. Animal weight was 182-197 g for males and 164-173 g for females. Animals were observed for mortality and clinical signs for 15 days.

Results

Value:	LD_{50} is greater than 5 g/kg
Mortality rate:	No mortality
Remarks:	All animals appeared normal with no incidence of clinical signs of toxicity. All animals gained weight normally. No treatment-related changes were noted at necropsy from gross pathological examination.

Conclusions

Remarks:	The acute oral LD_{50} is greater than 5 g/kg.

Data Quality

Reliability:	2D
Remarks:	The study is reliable with restrictions. Data appear solid, but report lacks details consistent with a guideline study.

Reference

Shepard, K. P. 1989. Acute toxicity of HQEE. Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY. HAEL No. 89-0126.

Other

Acute Toxicity – Entry 2 of 2

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	Not stated
Remarks:	None

Method

Method/guideline followed:	Not stated
Type:	Dermal toxicity
GLP:	Yes
Year:	1989
Species/Strain:	Rat/Crl:CD (SD)BR
Sex:	Male/Female
Number of animals/ Sex/dose:	5
Vehicle:	Water. Test article was moistened with the vehicle.
Route of administration:	Dermal
Remarks:	One group of 10 rats (5M,5F) was administered the test substance (solid material moistened with water) at a dose of 2 g/kg. The test article was applied to the skin following hair removal with an electric clipper. An occlusive wrap was used to hold the test material against the skin for 24 hours. At the end of exposure, residual test material was washed off with water. Animal weight was 187-197 g for males and 169-191 g for females. Animals were observed for mortality and clinical signs for 14 days.

Results

Value:	LD_{50} is greater than 2 g/kg.
Mortality rate:	No mortality
Remarks:	All animals appeared normal with no incidence of clinical signs of toxicity. All animals gained weight normally. No treatment-related changes were noted at necropsy from gross pathological examination.

Conclusions

Remarks:	The acute dermal LD_{50} is greater than 2 g/kg.

Data Quality

Reliability

(Klimisch):	2D
Remarks:	The study is reliable with restrictions. Data appear solid, but report lacks details consistent with a guideline study.
Reference	Shepard, K. P. 1989. Acute toxicity of HQEE. Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY. HAEL No. 89-0126.
Other	

B. Genetic Toxicity *In Vitro*– Entry 1 of 3

Test Substance

Identity:	Hydroquinone monomethyl ether (HQMME)(CAS RN 150-76-5) serving as an analog to Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	Reported as greater than 97%
Remarks:	None

Method

Method:	Ames/*Salmonella* Bacterial Point Mutation Assay
Type:	Reverse mutation assay
Test system:	Bacteria
GLP:	Not stated
Year:	1980
Species/Strain:	*Salmonella typhimurium/* TA98, TA100 and TA1535 and TA1537
Metabolic activation:	Test conducted with and without metabolic activation.
Concentrations tested:	3 µmol/plate
Remarks:	Method used was analogous to OECD TG 471. The test article was tested in spot tests using histifine-requiring mutants of *S. typhimurium*.

Conclusions

Remarks:	The test substance did not induce mutations in this test system with and without metabolic activation.

Data Quality

Reliability:	2C
Remarks:	Reliable without restriction; comparable to guideline study.

Reference Florin, I., Rutberg, L., Curvall, M. and Enzell, C. R. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicol. 18: 219-232.

Other

Genetic Toxicity *In Vitro*– Entry 2 of 3

Test Substance

Identity:	Hydroquinone monomethyl ether (HQMME)(CAS RN 150-76-5) serving as an analog to Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	Not stated
Remarks:	None

Method

Method:	Directive 84/449/EEC, B.14
Type:	Ames/*Salmonella* Bacterial Point Mutation Assay
Test system:	Reverse mutation assay
Species/Strain:	*Salmonella typhimurium/* TA100 and TA1530.
GLP:	Not stated
Year:	1980
Metabolic activation:	Test conducted with and without metabolic activation.
Concentrations tested:	Tested up to 4 µmoles/plate
Remarks:	Hydroquinone monomethyl ether was tested using the plate incorporation method at concentrations up to 4 µmoles/plate in strains TA100 and TA1530 with phenobarbitone sodium-induced OF-1 mouse liver S9 mix. *S. typhimurium* strains TA100 and TA1530 were provided by Professor B. N. Ames, Berkeley, CA. The capability for induction of mutations in the TA 100 strain was confirmed by using methylmethane sulphonate and in TA1530 strain by using N-nitroso-N'-nitro-N-methylguanidine. Hydroquinone monomethyl ether was obtained from Merck-Schuchardt, Darmstadt, Germany. Adult male OF-1 mice (30-40 g) were bred either in the IARC laboratory or were obtained from Iffa-Credo, St. Germain-sur-l'Arbresle, France. They were fed on a Charles River CFR diet. Groups of 2-6 animals received phenobarbitone sodium (PB), 1 mg/ml in the drinking water for 7 days before the experiment. A 9000 x g post-mitochondrial supernatant fraction (S9) was prepared at 0-4^{o} C from the pooled livers of the animals by centrifugation of a homogenate (3 ml of 0.15 M KCl/5 mM Sorensen buffer, pH 7.4, per gram of wet liver). The resulting fractions were kept at 0-4^{o} C for less than 2 hours and then used or

stored at –70° C for up to 3 weeks before use. All procedures were carried out with sterile glassware and solutions.

Plate-incorporation assay: The test compound, dissolved in 100 µl DMSO, 0.5 ml of a mixture containing various amounts of tissue S9 (normally up to 150 µl), cofactors (2 µmol $NADP^+$ and 2.5 µmol G6P), 4 µmol magnesium chloride, 50 µmol Sorenson phosphate buffer, pH 7.4, and 0.1 ml of a suspension containing 1-2 x 10^8 bacteria were combined with 2 ml histidine-poor soft agar (0.55%w/v agar, 0.55% w/v sodium chloride, 45.5 µM each of biotin and histidine, in 5 mM Sorensen buffer, pH 7.4). The agar mixture (final volume, 2.7 ml) was agitated vigorously and immediately porued onto plates of minimal agar; these were then incubated at 37° C. The number of *his*$^+$ revertant colonies was counted, usually after incubation for 48 hours. The presence of a backgrould lawn of bacteria on the histidine-poor soft agar plate was used as an indication that gro

Results

Result: Hydroquinone monomethyl ether did not induce mutations in this test system with or without metabolic activation.

Data Quality

Reliability: 2C

Remarks: Reliable with restriction; Only 2 strains of *S. typhimurium* were used.

Reference

Bartsch, H., Malaveille, C. and Camus, A-M. 1980. Validation and comparative studies on 180 chemicals with *S. typhimurium* strains and V79 Chinese hamster cells in the presence of various metabolizing systems. Mut. Res. 76: 1-50.

Other

Genetic Toxicity *In Vitro*– Entry 3 of 3

Test Substance

Identity:	Hydroquinone monomethyl ether (HQMME)(CAS RN 150-76-5) serving as an analog to Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	Not stated
Remarks:	None

Method

Method:	Not stated
Type:	Micronucleus assay
Test system:	*in vivo* using Sprague-Dawley rats
GLP:	Not stated
Year:	1997
Route of administration:	Dermal
Exposure period:	6 months
Test substance:	2% hydroquinone monomethyl ether and 0.01% All-Trans Retinoic Acid solution in ethanol (77.8%)
Concentrations tested:	Not stated
Statistical methods:	Not stated

Results

Result:	The test formulation did not induce micronuclei.

Data Quality

Reliability:	4B. Data were summarized in FDA documents as part of an NDA submission and minimal details were available.

Reference

USFDA. FDA Center for Drug Evaluation and Research Application Number 20-922. Pharmacology review(s). Evaluation of Pharmacology and Toxicology Data, Division of Dermatologic and Dental Drug Productd, HFD-540. Submitted 12/30/97. http://www.fda.gov/cder/foi/nda/99/20-922_Solage.htm.

Other

C. Repeated Dose Toxicity

Test Substance

Identity:	Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	97.2% -- determined by gas chromatography with flame ionization detector
Remarks:	Stability of the test article in the diets was determined by repeated analysis on 0, 4, and 8 days and 2, 3, 4, and 5 weeks after diet preparation. Concentrations of the test article were (mean ± SD) 0.1 ± 0.02 % and 0.96 ± 0.03 % after 36 days of storage indicating the material was stable for the duration of the study. Target concentrations were 0.1 % and 1.0 %. Mean (± SD) concentrations of the diets used during the study were 0.099 ± 0.0008, 0.32 ± 0.02, and 0.98 ± 0.03 %.

Method

Method/guideline followed:	OECD TG-407
Test type:	Oral
GLP:	Yes
Species:	Rat
Strain:	CD(SD)BR
Number and sex:	5 males and 5 females/group. Weight (mean ± SD) at the start of the study for males and females was 162 ± 6 g and 146 ± 6 g, respectively.
Route of administration:	Oral (incorporation into the diet)
Duration of test:	28 days
Concentration level:	0.1, 0.3 or 1.0% (rounded) in the feed. The concentrations correspond to dose levels of 85, 249 or 848 mg/kg/day in the males and 81, 262 or 851 mg/kg/day in the females, respectively.
Exposure period:	28 days
Frequency of treatment:	Test article was continuously available throughout the 28 day exposure period.
Control group and treatment:	Yes; concurrent using diets containing 1% corn oil.
Post-exposure observation period:	None

Methods:	Body weights were collected on days 0, 3, 7, 14, 21 and 28. Feed consumption was determined on days 3, 7, 10, 14, 17, 21, 24 and 28. Clinical observations were performed daily and included, but were not limited to, examination of fur, skin, eyes, motor activity, feces and urine. Blood was collected at necropsy for hematology (hemoglobin concentration, hematocrit, red and white blood cell count, differential white blood cell count, platelet count, red blood cell indices (MCV, MCH, and MCHC) and examination of blood smears for cellular morphology and clinical chemistry (aspartate aminotransferase, alanine aminotransferase, sorbitol dehydrogenase, alkaline phosphatase, creatining, urea nitrogen (BUN), and glucose) tests. Organ weights were taken for liver, kidneys, adrenal glands, testes, spleen, and thymus. The following tissues from the control and high dose groups were fixed in formalin and examined histopathologically: trachea, lungs, heart, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, pancreas, liver, salivary glands, kidneys, urinary bladder, pituitary gland, adrenal glands, thyroid gland, parathyroid glands, thymus, spleen, mesenteric lymph nodes, bone marrow (femor), brain, testes, epididymides, male accessory sex glands, ovaries, vagina, uterus, fallopian tubes, and gross lesions. Mean values were calculated for body weight, feed consumption, organ weights, hematology and clinical chemistry. All mean data, except feed consumption, were evaluated using the following computer-generated statistical tests: Bartlett's test ($p \leq 0.01$), one-way analysis of variance ($p \leq 0.05$) and Duncan's multiple range test ($p \leq 0.05$) to indicate statistical significance. Feed consumption was not analyzed statistically because the animals were group housed.
Remarks:	Protocol written and followed as per stated guideline with no deviations.

Results

NOAEL (NOEL):	Male rats – 0.3 % in the diet (249 mg/kg) Female rats – 1.0 % in the diet (851 mg/kg)
LOAEL (LOEL):	Male rats – 1.0 % in the diet (848 mg/kg) Female rats – Could not be determined as the NOAEL was the highest dose tested.

Remarks: No mortality occurred during the study. There were no treatment-related clinical signs of toxicity observed during the study. There were no statistical body weight differences between any of the treated animals and control animals. Feed consumption was comparable for all animals in the treated groups and control group. In the mid-dose males hemoglobin concentration was slightly higher compared to the control males (P=0.05), but there was no dose response relationship as the hemoglobin concentration in the low- and high-dose males was not statistically significantly different from controls. The mean blood platelet count for the high-dose males was slightly less (p=0.02) than for the control group. Platelet counts were not statistically significantly different from controls in the mid- and low-dose males. No other abnormalities in hematology were noted in the males. No hematological abnormalities were observed in any of the female animals. The clinical chemistry findings in all treated animals were comparable to controls. Relative kidney weights in low- and mid-dose females were lower (p=0.02), but not different from controls in the high-dose females. Absolute kidney weights for all treated female animals were similar to controls. No other organ weight differences were seen in any dose group for either sex. No compound-related lesions were seen during gross or histopathological examinations.

Conclusions

Remarks: The test article appears to reduce the platelet count in males at the top dose (848 mg/kg). 249 mg/kg is the NOEL for this effect. The decrease in relative kidney weights in the low- and mid-dose females is judged to be of no toxicological significance for 3 reasons. Absolute kidney weights were not affected in any of treated female animals, relative kidney weights were not different from controls in the high-dose females, and no gross or histopathological change was noted in this organ from any treatment group.

Data Quality

Reliability

(Klimisch):	1A
Remarks:	Reliable with restrictions. Guideline study (OECD TG-407)
Reference:	Hosefeld, R. S. and G. J. Hankinson. 1988. Four Week Oral Toxicity Study of Hydroquinone Bis (2-Hydroxyethyl) Ether in the Rat. Report number 87-0068. Toxicological Sciences Laboratory, Eastman Kodak Company, Rochester, NY 14650.

Other

D. Toxicity to Reproduction – Entry 1 of 2

Test Substance

Identity:	Hydroquinone monomethyl ether (HQMME)(CAS RN 150-76-5) serving as an analog to Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	Not stated
Remarks:	The test substance was a clinical formulation of 2 % hydroquinone monomethyl ether and 0.01 % tretinoin (all-trans retinoic acid)

Method

Method/guideline followed:	Not stated
Test type:	Dermal exposure
GLP:	Yes
Species:	Rat
Strain:	Crl:CD(SD)BR
Number and sex:	4 groups of 25 pregnant females/group
Route of administration:	Dermal
Duration of test:	Not stated specifically, but F_0, F_1 and F_2 generations were evaluated.
Dose level:	Vehicle (6.0 ml/kg/day), 0.6, 2.0, or 6.0 ml/kg/day (12/0.06, 40/0.2, or 120/0.6 mg/kg/day of HQMME/tretinoin, respectively).
Exposure period:	Exposure to the F_0 generation only for 35 days.
Frequency of treatment:	The test article was applied once daily, topically to clipped areas of the skin of the back (approximately 10 % of body surface area), unoccluded (except during lactation) for 6 hours/day from day 6 of gestation through lactation day 20 (F_0 animals only).
Control group and treatment:	Yes; concurrent using vehicle of ethyl alcohol, polyethylene glycol 400, butylated hydroxytoluene, ascorbic acid, citric acid, ascorbyl palmitate, disodium EDTA and purified water.
Methods:	25 pregnant females/group, approximately 12 weeks old at the time of breeding, were collared and exposed to the test article as described above in the frequency of treatment section. The dams were allowed to deliver naturally, and the litters were monitored. At post-natal day 4, litters were culled

to 8 pups each (4/sex when possible). At 8-13 days of age, 25 male and 25 female F_1 pups/group were randomly selected for evaluation of physical and functional development and reproductive performance. Of those, 10/sex/group were selected for evaluation of sensory function and behavioral testing (motor activity, learning, memory). F_1 animals were mated; females underwent laparotomy on gestation day 20, and F_2 fetuses were evaluated. F_1 males were necropsied after F_1 females.

Results

NOAEL (NOEL): 40/0.02 mg/kg/day (HQMME/tretinoin, respectively) for maternal, neonatal and developmental effects.

Remarks: No mortality occurred during the study. During the first week of lactation, all dams and offspring in the high dose group were euthanized due to extreme irritation at the application site.
Clinical signs – In F_0 animals, dose-related irritation was noted in treated groups, consisting of very slight to severe erythema (first noted on study day 8), very slight to moderate edema, including fissuring (especially at the high dose), desquamation (first noted on study day 13), eschar, focal eschar and exfoliation (first noted on study day 14) at the treatment sites. Vocalization was observed on application of the test material in mid- and high dose groups. High dose animals exhibited significant decreases in body weight on gestation day 20 and lactation day 1, in mean body weight gain during gestation, and in food consumption during gestation days 9-12. Increased food consumption in first few days of lactation was observed in those animals before they were sacrificed for humane reasons. In F_1 animals, drug-related changes were only observed at the maternally toxic high dose. In that group, there was increased pup mortality, decreased pup body weight, and an increased incidence of clinical signs; signs seen in high dose pup included small size, hypoactivity, cool to the touch, and pale in appearance. As adults F_1 males from treated groups exhibited body weights that appeared body weights that appeared to lag behind those of controls in a dose-dependent manner, but that finding was not

statistically significant. There was no apparent effect on male body weight gain at any dose. No significant effect was seen on body weight, body weight gain, gestation body weight or gestation body weight gain in females.

Reproductive parameters – Six dams each in the mid- and high dose groups failed to deliver by post-mating day 25, as compared to two each in the control and low dose groups. Four high dose females had total litter loss between lactation days 1 and 5. Reduced F_1 pup survival and a higher rate of missing or cannibalized pups were seen in high dose litters after post-natal day (PND) 1. High dose F_1 pups had reduced body weights, and there was an increased incidence of F_1 pup clinical and necropsy findings. Developmental parameters were included in F_1 pup observations. Balanopreputial separation and vaginal patency were unaffected by treatment, although females in treated groups appeared to lag behind controls in timing of the latter measure, but not in a dose-related manner. Auditory startle testing on or about PND 21 and 60 revealed no treatment-related effects. Motor activity (total and ambulatory) measurements were made on or about PND 13, 17, 21 and 60. On PND 13 there was apparently less activity in treated groups, but the variability was so great in controls at this time point that there was no significant difference. It is likely that this is too early an age for motor activity to be a sensitive measure. Variability was too high at PND 17 and 21 for meaningful interpretation as well. At PND 60, variability was less and there was no effect of treatment on total or ambulatory counts. Testing in the water maze was initiated between PND 20-23 and between PND 57-62. Swimming ability, learning and memory was evaluated. No effect of treatment was observed. Estrous cycling in F_1 females and reproductive performance in F_1 animals was unaffected by treatment. Gravid uterine weights and F_2 fetuses were also unaffected. There did appear to be an increase in early resorptions, and therefore, post-implantation loss in treated groups compared to controls. It was not statistically significant.

Examination of Pathological Change – On gross necropsy, the only treatment-related finding in F_0

dams was reddening, thickening and scabbing of skin at treated sites. In F_1 pups found dead or euthanized, gross findings in the high dose group included absence of milk in the stomach, renal papilla not developed or not fully developed and/or ureters or urinary bladder were distended. Also, at the high dose there was one pup in one litter with a hemorrhagic ring around the iris. In F_1 adults, no significant findings were seen that could be attributed to treatment. One low dose female had an enlarged spleen and one mid-dose female had clear fluid in one uterine horn. In F_2 pups, two low dose fetuses in two different litters had external malformations (one with omphalocele and a second with craniorachischisis and a curly tail). These were considered to be within the range of historical controls. No external malformations were observed in the mid-dose group.

Data Quality

Reliability (Klimisch): 2B

Remarks: Valid with restrictions; Data were summarized in FDA documents as part of an NDA submission. While original report was not available, the study was summarized in significant detail.

Reference:

FDA Center for Drug Evaluation and Research Application Number 20-922. Dermal Study of Pre- and Post-natal Development in the Rat. Pharmacology review(s). Study number 96670. Evaluation of Pharmacology and Toxicology Data, Division of Dermatologic and Dental Drug Products, HFD-540. Submitted 12/30/97. http://www.fda.gov/cder/foi/nda/99/20-922_Solage.htm

Toxicity to Reproduction – Entry 2 of 2

Test Substance

Identity:	Hydroquinone monomethyl ether (HQMME)(CAS RN 150-76-5) serving as an analog to Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	Not stated
Remarks:	The test substance was a clinical formulation of 2 % hydroquinone monomethyl ether and 0.01 % tretinoin (all-trans retinoic acid)

Method

Method/guideline followed:	Not stated
Test type:	Dermal exposure
GLP:	Yes
Species:	Rat
Strain:	Crl:CD(SD)BR
Number and sex:	4 groups of 25 rats/sex/group
Route of administration:	Dermal
Duration of test:	9 weeks
Dose level:	Vehicle (4 ml/kg/day), 1, 2, or 4 ml/kg/day (20/0.1, 40/0.2, or 80/0.4 mg/kg/day of HQMME/tretinoin, respectively).
Exposure period:	Exposure of males and females prior to mating and during gestation.
Frequency of treatment:	The test article was applied once daily, topically to clipped areas of the skin of the back (approximately 10 % of body surface area), unoccluded for 6 hours/day. Males were dosed for 4 weeks and females for 2 weeks prior to mating. Males and females were dosed throughout the cohabitation period for a maximum of 3 weeks. Females were dosed through gestation day 7, then sacrificed on gestation day 15. Males were dosed through the day before the scheduled sacrifice.
Control group and treatment:	Yes; concurrent using vehicle of ethyl alcohol, polyethylene glycol 400, butylated hydroxytoluene, ascorbic acid, citric acid, ascorbyl palmitate, disodium EDTA and purified water.
Methods:	25 animals/sex/group, approximately 12 weeks old at the time of breeding, were collared and exposed

to the test article as described above in the frequency of treatment section. Males were paired with females in the same treatment group on a 1:1 basis. Laparotomies were performed on females on gestation day 15.

Results

NOAEL (NOEL): The parental systemic NOAEL was determined to be 40/0.2 mg/kg/day. The NOEL for dermal irritation was less than 20/0.1 mg/kg/day. The NOAEL for reproductive performance was considered to be greater than 80/0.4 mg/kg/day. The test formulation was not considered to be a reproductive toxicant in this study.

Remarks: One male in the control group died on study day 11. Clinical signs – No systemic signs were observed. Body weight was decreased in high dose males on days 17-59 and was statistically significantly lower than controls on days 24-56. Body weight gains were decreased from study days 0-7, 10-24, 35-38, 42-45, and 49-52 in high dose males. Dose-related dermal irritation was observed in all treated groups, consisting of slight to severe erythema and edema, eshcar, fissuring (males only), desquamation, and exfoliation. Sporadic vocalization occurred in mid- and high dose animals when dosed. No dermal effects were seen in vehicle control animals. Reproductive parameters – In males, mating and fertility parameters, sperm evaluation, and gonadal weights were not affected by treatment. Histological examination of the testes revealed no treatment-related changes. In females, estrous cycling, mating, fertility and intrauterine parameters were not affected by treatment. Intrauterine survival of F_1 embryos was comparable between treated and control groups. Pre-implantation loss was slightly increased at the high dose relative to control, but the difference was not significant, and the measure was within the range of historical controls for the contract laboratory. Post-implantation loss and mean numbers of viable embryos, corpora lutea and implantation sites were similar in treated and control groups. Pre-coital intervals were not affected by treatment. Organ weights – Testicular weights appeared to be decreased in high dose males; statistical

significance was seen only for the absolute weight of the right testis, but not for the relative weight. This finding may be attributable to the final body weight being lower than control. Mean ovarian weights (absolute and relative) were decreased in mid-dose females, and absolute ovarian weight in high dose females appeared lower than control, but the latter was not statistically significant. Since there was no dose-related trend, this was not considered to be an effect of treatment. It was concluded that these above differences were not treatment related. Therefore, no treatment-related effects were observed in brain, pituitary gland, ovary, or testis/epididymis weights.

Data Quality

Reliability (Klimisch): 2B

Remarks: Valid with restrictions; Data were summarized in FDA documents as part of an NDA submission. While original report was not available, the study was summarized in significant detail.

Reference: FDA Center for Drug Evaluation and Research Application Number 20-922. Dermal Study of Fertility and Early Embryonic Development in Rats. Pharmacology review(s). Study number 96672. Evaluation of Pharmacology and Toxicology Data, Division of Dermatologic and Dental Drug Products, HFD-540. Submitted 12/30/97. http://www.fda.gov/cder/foi/nda/99/20-922_Solage.htm

E. Developmental Toxicity – Entry 1 of 3

Test Substance

Identity:	Hydroquinone monomethyl ether (HQMME)(CAS RN 150-76-5) serving as an analog to Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	Not stated
Remarks:	The test substance was a clinical formulation of 2 % hydroquinone monomethyl ether and 0.01 % tretinoin (all-trans retinoic acid)

Method

Method/guideline followed:	Not stated
Test type:	Dermal exposure
GLP:	Yes
Species:	Rat
Strain:	Crl:CD(SD)BR
Number and sex:	4 groups of 25 rats/group
Route of administration:	Dermal
Duration of test:	3 weeks
Dose level:	Vehicle (4 ml/kg/day), 1, 2, or 4 ml/kg/day (20/0.1, 40/0.2, or 80/0.4 mg/kg/day of HQMME/tretinoin, respectively).
Exposure period:	Exposure of females on days 6-15 of gestation.
Frequency of treatment:	The test article was applied once daily, topically to clipped areas of the skin of the back (approximately 10 % of body surface area), unoccluded for 6 hours/day.
Control group and treatment:	Yes; concurrent using vehicle of ethyl alcohol, polyethylene glycol 400, butylated hydroxytoluene, ascorbic acid, citric acid, ascorbyl palmitate, disodium EDTA and purified water.
Methods:	25 pregnant animals/group, approximately 12 weeks old at the time of breeding, were collared and exposed to the test article as described above in the frequency of treatment section. Laparotomy was performed on gestation day 20 to examine reproductive organs and fetuses.

Results

NOAEL (NOEL): The systemic maternal NOAEL was 40/0.2 mg/kg/day based on body weight changes. The NOAEL for developmental toxicity was greater than 80/0.4 mg/kg/day. The test formulation was determined not to be a developmental toxicant in this study.

Remarks: There were no deaths in the study.
Clinical signs – The dams exhibited no systemic signs of toxicity. Treated animals did exhibit dose-related irritation consisting of very slight to slight erythema and desquamation in all treated groups. The incidence of the latter was increased in the high dose group. Local irritation was resolved in many animals by gestation day 20. Eschar was noted in one high dose animal on gestation days 19 and 20. Control animals were unaffected. The mean body weight in the high dose group was reduced and was significantly different from control on gestation days 12-16. Control animals were unaffected. The mean body weight in the high dose group was reduced and was significantly different from control on gestation days 12-16. A significant decrease in body weight gain was observed in high dose animals on gestation days 6-12, and food consumption in that group was decreased during the entire treatment period. Also in the high dose group, net body weight and net body weight gain were reduced, but gravid uterine weight was comparable to that of control animals.
Reproductive/fetal parameters – Intrauterine growth ad survival were concluded to be unaffected by treatment. One high dose female did have 6 dead fetuses and 2 late resorptions, but these were attributed to infections. Mean fetal body weight was slightly decreased in the high dose group due to the one female with pathologic intrauterine abnormalities and a resulting low mean litter weight. However, there were no indications of growth retardation, and the mean fetal body weight in that group was not significantly different from control when that litter was excluded. The test article was not implicated. Interestingly, even with the exclusion of that litter, fetal body weights for male pups were significantly reduced at the high dose. No significant differences were seen in

numbers of corpora lutes and implantation sites. No external malformations or variations were seen. Visceral malformations were noted in one fetus each in control (ventricular septal defect) and high dose (situs inversus) groups. No visceral variations were noted. A skeletal malformation was found in one fetus in the low dose group (vertebral anomaly). Skeletal variations were similar in incidence and type in all groups. Those fetal malformations and variations observed were considered to be spontaneous and not related to treatment. Examination of pathological change – At necropsy, one high dose female had clear fluid in the uterus and a second had greenish uterine fluid, 6 dead fetuses and 2 late resorptions. The latter was considered unusual and probably related to infection. Findings of pathological change in a few low and mid-dose females did not appear to be related to treatment.

Data Quality

Reliability (Klimisch): 2B

Remarks: Valid with restrictions; Data were summarized in FDA documents as part of an NDA submission. While original report was not available, the study was summarized in significant detail.

Reference: FDA Center for Drug Evaluation and Research Application Number 20-922. Pharmacology review(s). Dermal Study of Embryo-fetal Development in Rats. Study number 96671. Evaluation of Pharmacology and Toxicology Data, Division of Dermatologic and Dental Drug Products, HFD-540. Submitted 12/30/97. http://www.fda.gov/cder/foi/nda/99/20-922_Solage.htm

Developmental Toxicity – Entry 2 of 3

Test Substance

Identity:	Hydroquinone monomethyl ether (HQMME)(CAS RN 150-76-5) serving as an analog to Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	Not stated
Remarks:	The test substance was a clinical formulation of 2 % hydroquinone monomethyl ether and 0.01 % tretinoin (all-trans retinoic acid)

Method

Method/guideline followed:	Not stated
Test type:	Dermal exposure
GLP:	Yes
Species:	Rabbit
Strain:	New Zealand White [Hra:(NZW)SPF]
Number and sex:	5 groups of 20 rabbits/group
Route of administration:	Dermal
Duration of test:	4 weeks
Dose level:	Untreated control, vehicle (2 ml/kg/day), 0.2, 0.6, or 2.0 ml/kg/day (4/0.02, 12/0.06, or 40/0.2 mg/kg/day of HQMME/tretinoin, respectively).
Exposure period:	Exposure of females on days 6-18 of gestation.
Frequency of treatment:	The test article was applied once daily, topically to clipped areas of the skin of the back (approximately 10 % of body surface area), unoccluded for 6 hours/day.
Control group and treatment:	Yes; concurrent using vehicle of ethyl alcohol, polyethylene glycol 400, butylated hydroxytoluene, ascorbic acid, citric acid, ascorbyl palmitate, disodium EDTA and purified water.
Methods:	20 pregnant animals/group, conducted as two consecutive replicate experiments with groups of 10 animals each. Animals were restrained in stocks during exposure to the test article for 6 hours/day. The application sites were then washed with warm water and soap and dried. The rabbits were collared with Elizabethan collars and returned to clean cages. Caesarean sections were performed on

gestation day 29 to examine reproductive organs and fetuses.

Results

NOAEL (NOEL): A NOEL for teratogenicity in this study was established at 4/0.02 mg/kg/day. This NOEL was due to the effect of tretinoin. The NOEL for teratogenicity of HQMME in rabbits should be considered to be 40 mg/kg/day.

Remarks: One dam in the vehicle control group died due to causes unrelated to treatment.
Clinical signs – Significant dose-related irritation of the skin was seen. Erythema was observed in the vehicle control group and the treated groups and was dose-related in severity. Dose-related edema was seen in all treatment groups. Dose-related desquamation and fissuring were seen in the mid- and high dose groups. A low incidence of desquamation was noted in the vehicle control group, but was not statistically significant. Atonia and hyperreactivity were seen in the high dose group. The maximum grades for all indices of irritation were described as moderate. Other clinical observations included abnormal feces, red substance in the cage pan, head tilt, vocalization, and red substance in the urine. The incidence of these findings was not dose-related.
Reproductive/fetal parameters – Abortions occurred in all groups in a manner unrelated to dose: 3, 2, 3, 4 and 3 in each of the untreated control, vehicle control, low, mid-, and high dose groups, respectively. Premature delivery on gestation day 29 occurred in one animal in each of the untreated control and vehicle control groups. No information from these litters or from litters from animals found dead or euthanized in extremis was included in fetal and litter evaluations. There were no significant differences in the numbers of corpora lutea or implantation sites, litter size, live fetuses, early or late resprptions, fetal body weights, sex ratios, or post-implantation loss. There were no dead fetuses in any group. Pre-implantation loss appeared slightly higher in the high dose group. Fetal evaluations were made from 16, 15, 17, 16 and 17 litters in the untreated control, vehicle control, low, mid-, and high dose groups, respectively. The

incidence of total alterations was similar across litters. Ten fetuses in six litters in the mid-dose group exhibited a variation in skull ossification described as displaced nasal midline suture. Statistically, this was significantly increased in the fetuses. In the high dose group 3 fetuses in 2 litters had irregularly shaped scapular alae. This was a statistically significant finding. Alterations to thoracic vertebrae appeared to be of significantly higher incidence in the high dose group. Marked hydrocephaly with visible doming of the head was observed in one mid-dose litter and two fetuses in one high dose litter. These were not statistically significant, but were considered treatment-related and due to the known effects of tretinoin. Evaluation of pathological change – At necropsy, none of the findings in the dams were dose-dependent. Findings included clear gelatinous material in the stomach, light green caseous material adhered to the indometrium in the uterine horn, gas distention in the gastrointestinal tract, red brown or brown perivaginal substance, and green brown, red brown, or brown perianal substance.

Data Quality

Reliability (Klimisch): 2B

Remarks: Valid with restrictions; Data were summarized in FDA documents as part of an NDA submission. While original report was not available, the study was summarized in significant detail.

Reference: FDA Center for Drug Evaluation and Research Application Number 20-922. Pharmacology review(s). Dermal Study of Pre- and Post-natal Development in Rabbits. Study number 98612. Evaluation of Pharmacology and Toxicology Data, Division of Dermatologic and Dental Drug Products, HFD-540. Submitted 12/30/97. http://www.fda.gov/cder/foi/nda/99/20-922_Solage.htm

Developmental Toxicity – Entry 3 of 3

Test Substance

Identity:	Hydroquinone monomethyl ether (HQMME)(CAS RN 150-76-5) serving as an analog to Hydroquinone bis (2-hydroxyethyl) ether (CAS RN 104-38-1)
Purity:	Not stated

Method

Method/guideline followed:	Not stated
Test type:	Dermal exposure
GLP:	Not stated
Species:	Rat
Strain:	Albino
Number and sex:	5 groups of 10-12 rats/group
Route of administration:	Dermal
Duration of test:	3 weeks
Dose level:	Untreated control, vehicle control (bleach crème base), 5 % HQMME and 1 % ascorbylpalmitate in bleach crème base,25 % HQMME, or 5 % ascorbylpalmitate in water-oil emulsions.
Exposure period:	Exposure of females daily on days 1-20 of gestation.
Methods:	The animals were sacrificed shortly before scheduled parturition. Time of delivery, number of live/stillborn offspring, and the number of malformed fetuses were recorded.

Results

Remarks:	No significant differences were observed between treated and control groups with respect to skeletal anomalies, post-implantation mortality, craniocaudal dimensions and weight of embryos, or placental weights. No teratogenic effects of bleaching crème, or its components (HQMME and ascorbylpalmitate), were detected. Both test items produced increased pre-implantation mortality to embryos.

Data Quality

Reliability (Klimisch):	4A

Remarks:	Not assignable; information was available only in abstract.
Reference:	Akhabadze, A. F., Koroleva, N. B., and Kovanova, E. K. 1981. Experimental study of substances containing para-groups used in cosmetics applied epicutaneously. Vestn. Dermatol. Venerol. 6, 23-27.